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NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
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NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
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NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	28	Oct 21	EVENTLINE has been reloaded
NEWS	29	Oct 24	BEILSTEIN adds new search fields
NEWS	30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS	32	Nov 18	DKILIT has been renamed APOLLIT
NEWS	33	Nov 25	More calculated properties added to REGISTRY
NEWS	34	Dec 02	TIBKAT will be removed from STN
NEWS	35	Dec 04	CSA files on STN
NEWS	EXPRESS		October 14 CURRENT WINDOWS VERSION IS V6.01, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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L1 619 (BERKENSTAM-A? OR BERTILSSON-G? OR POELLINGER-L?)/AU

=> s l1 and (hypoxia or PAS or IPAS)

L2 124 L1 AND (HYPOXIA OR PAS OR IPAS)

=> s l2 and py<=2000

2 FILES SEARCHED...

3 FILES SEARCHED...

L3 78 L2 AND PY<=2000

=> dup rem l3

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L4 20 DUP REM L3 (58 DUPLICATES REMOVED)

=> d ibib abs 1-20

L4 ANSWER 1 OF 20

MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2000138193 MEDLINE

DOCUMENT NUMBER: 20138193 PubMed ID: 10671489

TITLE: A redox mechanism controls differential DNA binding activities of **hypoxia**-inducible factor (HIF) 1alpha and the HIF-like factor.

AUTHOR: Lando D; Pongratz I; **Poellinger L**; Whitelaw M L

CORPORATE SOURCE: Department of Biochemistry, University of Adelaide, Adelaide 5005, South Australia.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Feb 18) 275 (7) 4618-27.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000321

AB **Hypoxia**-inducible factor 1alpha (HIF-1alpha) and the HIF-like factor (HLF) are two highly related basic Helix-Loop-Helix/Per-Arnt-Sim (bHLH/PAS) homology transcription factors that undergo dramatically increased function at low oxygen levels. Despite strong similarities in their activation mechanisms (e.g. they both undergo rapid **hypoxia**-induced protein stabilization, bind identical target DNA sequences, and induce synthetic reporter genes to similar degrees), they are both essential for embryo survival via distinct functions during vascularization (HIF-1alpha) or catecholamine production (HLF). It is currently unknown how such specificity of action is achieved. We report here that DNA binding by HLF, but not by HIF-1alpha, is dependent upon reducing redox conditions. In vitro DNA binding and mammalian two-hybrid assays showed that a unique cysteine in the DNA-binding basic region of HLF is a target for the reducing activity of redox factor Ref-1. Although the N-terminal DNA-binding domain of HIF-1alpha can function in the absence of Ref-1, we found that the C-terminal region containing the transactivation domain requires Ref-1 for full activity. Our data reveal that the **hypoxia**-inducible factors are subject to complex redox control mechanisms that can target discrete regions of the proteins and are the first to establish a discriminating control mechanism for differential regulation of HIF-1alpha and HLF activity.

L4 ANSWER 2 OF 20 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001008238 MEDLINE
DOCUMENT NUMBER: 20402336 PubMed ID: 10944113
TITLE: Mechanism of regulation of the **hypoxia**-inducible factor-1 alpha by the von Hippel-Lindau tumor suppressor protein.
AUTHOR: Tanimoto K; Makino Y; Pereira T; **Poellinger L**
CORPORATE SOURCE: Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institutet, S-171 77 Stockholm, Sweden.
SOURCE: EMBO JOURNAL, (2000 Aug 15) 19 (16) 4298-309.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020420
Entered Medline: 20001025

AB In normoxic cells the **hypoxia**-inducible factor-1 alpha (HIF-1 alpha) is rapidly degraded by the ubiquitin-proteasome pathway, and activation of HIF-1 alpha to a functional form requires protein stabilization. Here we show that the product of the von Hippel-Lindau (VHL) tumor suppressor gene mediated ubiquitylation and proteasomal degradation of HIF-1 alpha under normoxic conditions via interaction with the core of the oxygen-dependent degradation domain of HIF-1 alpha. The region of VHL mediating interaction with HIF-1 alpha overlapped with a putative macromolecular binding site observed within the crystal structure of VHL. This motif of VHL also represents a mutational hotspot in tumors, and one of these mutations impaired interaction with HIF-1 alpha and subsequent degradation. Interestingly, the VHL binding site within HIF-1 alpha overlapped with one of the minimal transactivation domains. Protection of HIF-1 alpha against degradation by VHL was a multistep mechanism, including **hypoxia**-induced nuclear translocation of HIF-1 alpha and an intranuclear **hypoxia**-dependent signal. VHL was not released from HIF-1 alpha during this process. Finally,

stabilization of HIF-1 alpha protein levels per se did not totally bypass the need of the hypoxic signal for generating the transactivation response.

L4 ANSWER 3 OF 20 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000063199 MEDLINE
DOCUMENT NUMBER: 20063199 PubMed ID: 10594042
TITLE: Redox-regulated recruitment of the transcriptional coactivators CREB-binding protein and SRC-1 to **hypoxia**-inducible factor 1alpha.
AUTHOR: Carrero P; Okamoto K; Coumailleau P; O'Brien S; Tanaka H; **Poellinger L**
CORPORATE SOURCE: Department of Cell and Molecular Biology, Karolinska Institutet, S-171 77 Stockholm, Sweden.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Jan) 20 (1) 402-15.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000110
AB **Hypoxia**-inducible factor 1alpha (HIF-1alpha) functions as a transcription factor that is activated by decreased cellular oxygen concentrations to induce expression of a network of genes involved in angiogenesis, erythropoiesis, and glucose homeostasis. Here we demonstrate that two members of the SRC-1/p160 family of transcriptional coactivators harboring histone acetyltransferase activity, SRC-1 and transcription intermediary factor 2 (TIF2), are able to interact with HIF-1alpha and enhance its transactivation potential in a **hypoxia**-dependent manner. HIF-1alpha contains within its C terminus two transactivation domains. The **hypoxia**-inducible activity of both these domains was enhanced by either SRC-1 or the CREB-binding protein (CBP)/p300 coactivator. Moreover, at limiting concentrations, SRC-1 produced this effect in synergy with CBP. Interestingly, this effect was strongly potentiated by the redox regulatory protein Ref-1, a dual-function protein harboring DNA repair endonuclease and cysteine reducing activities. These data indicate that all three proteins, CBP, SRC-1, and Ref-1, are important components of the **hypoxia** signaling pathway and have a common function in regulation of HIF-1alpha function in hypoxic cells. Given the absence of cysteine residues in one of the Ref-1-regulated transactivation domains of HIF-1alpha, it is thus possible that Ref-1 functions in hypoxic cells by targeting critical steps in the recruitment of the CBP-SRC-1 coactivator complex.

L4 ANSWER 4 OF 20 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001137976 MEDLINE
DOCUMENT NUMBER: 20544966 PubMed ID: 11091086
TITLE: Characterization and developmental expression of xSim, a Xenopus bHLH/**PAS** gene related to the Drosophila neurogenic master gene single-minded.
AUTHOR: Coumailleau P; Penrad-Mobayed M; Lecomte C; Bollerot K; Simon F; **Poellinger L**; Angelier N
CORPORATE SOURCE: Universite Pierre et Marie Curie, Groupe Genes et Developpement, UMR7622-CNRS Biologie Moleculaire et Cellulaire du Developpement, Universite Pierre et Marie Curie, Paris, France. pascal.coumailleau.@snv.jussieu.fr
SOURCE: MECHANISMS OF DEVELOPMENT, (2000 Dec) 99 (1-2) 163-6.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB We have isolated a novel gene from *Xenopus*, denominated xSim, which encodes a protein of 760 amino acids containing a basic helix-loop-helix (bHLH) motif contiguous to a PAS domain characteristic of an emerging family of transcriptional regulators so called bHLH/PAS. xSim shares a strong amino acid sequence identity with the *Drosophila* Single-minded (dSim) and with the murine Sim1 and Sim2 proteins. Phylogenetic analysis reveals that xSim gene is an ortholog gene of the mSim2 gene. Spatio-temporal analysis shows a maternal and a zygotic expression of xSim throughout early *Xenopus* development. In situ hybridization assays reveal that the transcripts are enriched in the animal hemisphere until blastula stage and extend to the marginal zone at early gastrula stage. As development proceeds, xSim is mainly restricted to the central nervous system.

L4 ANSWER 5 OF 20 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:375487 SCISEARCH
THE GENUINE ARTICLE: 194NL
TITLE: Evidence that the Co-chaperone p23 regulates ligand responsiveness of the dioxin (aryl hydrocarbon) receptor
AUTHOR: Kazlauskas A; Poellinger L; Pongratz I (Reprint)
CORPORATE SOURCE: KAROLINSKA INST, DEPT CELLULAR & MOL BIOL, S-17177 STOCKHOLM, SWEDEN (Reprint); KAROLINSKA INST, DEPT CELL & MOL BIOL, S-17177 STOCKHOLM, SWEDEN
COUNTRY OF AUTHOR: SWEDEN
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (7 MAY 1999)
Vol. 274, No. 19, pp. 13519-13524.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The dioxin (aryl hydrocarbon) receptor is a ligand-dependent transcription factor that induces expression of a number of genes encoding drug metabolizing enzymes. In the absence of ligand the dioxin receptor is present in the cytoplasmic compartment of the cell associated with the molecular chaperone hsp90, which has been implicated in regulating the correct folding of the ligand binding domain of the receptor. In this study we have examined a potential role of the hsp90-associated p23 protein in the activation process of the dioxin receptor to a DNA binding form. In an in vitro model we show that addition of ligand alone to the dioxin receptor fails to induce release of hsp90 from the dioxin receptor. In the presence of ligand, this release was, however, induced upon addition of purified preparations of Arnt. Interestingly, p23 was also found to be associated with the nonactivated form of the dioxin receptor. Following fractionation on sucrose gradients p23 was dissociated from the receptor-hsp90 complex generating a receptor form, which showed ligand-independent release of hsp90 by Arnt and, consequently, ligand-independent activation of the DNA binding activity of the dioxin receptor. Ligand dependence was reconstituted in the presence of molybdate, a transition metal ion known to stabilize the interaction between the molecular chaperone hsp90 and p23. Taken together these experiments suggest a role of p23 in modulating ligand responsiveness in the activation process of the dioxin receptor.

L4 ANSWER 6 OF 20 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1999240746 MEDLINE

DOCUMENT NUMBER: 99240746 PubMed ID: 10224119

TITLE: Repression of dioxin signal transduction in fibroblasts. Identification Of a putative repressor associated with Arnt.

AUTHOR: Gradin K; Toftgard R; **Poellinger L**; Berghard A

CORPORATE SOURCE: Department of Cell and Molecular Biology, Karolinska Institute, S-171 77 Stockholm, Sweden..
katarina.gradin@cmb.ki.se

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 May 7) 274 (19) 13511-8.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990603

AB Heterodimeric complexes of basic helix-loop-helix/**PAS** transcription factors are involved in regulation of diverse physiological phenomena such as circadian rhythms, reaction to low oxygen tension, and detoxification. In fibroblasts, the basic helix-loop-helix/**PAS** heterodimer consisting of the ligand-inducible dioxin receptor and Arnt shows DNA-binding activity, and the receptor and Arnt are able to activate transcription when fused to a heterologous DNA-binding domain. However, fibroblasts are nonresponsive to dioxin with regard to induction mediated by the DNA response element recognized by the receptor and Arnt. Here we demonstrate that Arnt is associated with a fibroblast-specific factor, forming a complex that is capable of binding the dioxin response element. This factor may function as a repressor since negative regulation of target gene induction appears to be abolished by inhibition of histone deacetylase activity by trichostatin A. Finally, the negative regulatory function of this factor appears to be restricted for dioxin signaling since Arnt was able to mediate, together with **hypoxia**-inducible factor-1alpha, transcriptional activation in hypoxic cells. Taken together, these data suggest that fibroblast-specific inhibition of dioxin responsiveness involves recruitment by Arnt of a cell type- and signaling pathway-specific corepressor associated with a histone deacetylase.

L4 ANSWER 7 OF 20 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 1999156935 MEDLINE

DOCUMENT NUMBER: 99156935 PubMed ID: 10037745

TITLE: Regulation of the **hypoxia**-inducible transcription factor 1alpha by the ubiquitin-proteasome pathway.

AUTHOR: Kallio P J; Wilson W J; O'Brien S; Makino Y; **Poellinger L**

CORPORATE SOURCE: Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institutet, S-171 77 Stockholm, Sweden.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Mar 5) 274 (10) 6519-25.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199903

ENTRY DATE: Entered STN: 19990413
Last Updated on STN: 20000303
Entered Medline: 19990330

AB HIF-1alpha (**hypoxia**-inducible factor 1alpha) is a

basic-helix-loop-helix **PAS** (Per/Arnt/Sim) transcription factor that, under hypoxic conditions, dimerizes with a partner factor, the basic-helix-loop-helix/**PAS** protein Arnt, to recognize **hypoxia**-responsive elements of target genes. It has recently been demonstrated that HIF-1alpha protein but not mRNA levels are dramatically up-regulated in response to **hypoxia**. Here we show that inhibitors of 26 S proteasome activity produced a dramatic accumulation of endogenous as well as transfected HIF-1alpha protein under normoxic conditions, whereas the levels of Arnt protein were not affected. HIF-1alpha was polyubiquitinated in vivo under normoxic conditions, indicating rapid degradation via the ubiquitin-proteasome pathway. This degradation process appeared to target a region within the C terminus of HIF-1alpha. Importantly, HIF-1alpha ubiquitination was drastically decreased under hypoxic conditions. Up-regulation of HIF-1alpha protein by proteasome inhibitors did not result in transcriptional activation of reporter genes, indicating either the requirement of additional regulatory steps to induce functional activity of HIF-1alpha or the inability of polyubiquitinated forms of HIF-1alpha to mediate hypoxic signal transduction. In support of both these notions, we demonstrate that HIF-1alpha showed **hypoxia**-dependent translocation from the cytoplasm to the nucleus and that this regulatory mechanism was severely impaired in the presence of proteasome inhibitors. Taken together, these data demonstrate that the mechanism of **hypoxia**-dependent activation of HIF-1alpha is a complex multistep process and that stabilization of HIF-1alpha protein levels is not sufficient to generate a functional form.

L4 ANSWER 8 OF 20 MEDLINE DUPLICATE 7
 ACCESSION NUMBER: 1999219869 MEDLINE
 DOCUMENT NUMBER: 99219869 PubMed ID: 10202154
 TITLE: Molecular mechanisms of transcription activation by HLF and HIF1alpha in response to **hypoxia**: their stabilization and redox signal-induced interaction with CBP/p300.
 AUTHOR: Ema M; Hirota K; Mimura J; Abe H; Yodoi J; Sogawa K; Poellinger L; Fujii-Kuriyama Y
 CORPORATE SOURCE: Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-77, Japan.
 SOURCE: EMBO JOURNAL, (1999 Apr 1) 18 (7) 1905-14. Journal code: 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199906
 ENTRY DATE: Entered STN: 19990614
 Last Updated on STN: 19990614
 Entered Medline: 19990601
 AB **Hypoxia**-inducible factor 1 alpha (HIF1alpha) and its related factor, HLF, activate expression of a group of genes such as erythropoietin in response to low oxygen. Transfection analysis using fusion genes of GAL4DBD with various fragments of the two factors delineated two transcription activation domains which are inducible in response to **hypoxia** and are localized in the C-terminal half. Their sequences are conserved between HLF and HIF1alpha. One is designated NAD (N-terminal activation domain), while the other is CAD (C-terminal activation domain). Immunoblot analysis revealed that NADs, which were rarely detectable at normoxia, became stabilized and accumulated at **hypoxia**, whereas CADs were constitutively expressed. In the mammalian two-hybrid system, CAD and NAD baits enhanced the luciferase expression from a reporter gene by co-transfection with CREB-binding protein (CBP) prey, whereas CAD, but not NAD, enhanced beta-galactosidase expression in yeast by CBP co-expression, suggesting that NAD and CAD interact with CBP/p300 by a different mechanism. Co-transfection

experiments revealed that expression of Ref-1 and thioredoxin further enhanced the luciferase activity expressed by CAD, but not by NAD. Amino acid replacement in the sequences of CADs revealed a specific cysteine to be essential for their **hypoxia**-inducible interaction with CBP. Nuclear translocation of thioredoxin from cytoplasm was observed upon reducing O2 concentrations.

L4 ANSWER 9 OF 20 MEDLINE DUPLICATE 8
 ACCESSION NUMBER: 1999043864 MEDLINE
 DOCUMENT NUMBER: 99043864 PubMed ID: 9822602
 TITLE: Signal transduction in hypoxic cells: inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the **hypoxia**-inducible factor-1alpha.
 AUTHOR: Kallio P J; Okamoto K; O'Brien S; Carrero P; Makino Y; Tanaka H; **Poellinger L**
 CORPORATE SOURCE: Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institutet, S-171 77 Stockholm, Sweden.
 SOURCE: EMBO JOURNAL, (1998 Nov 16) 17 (22) 6573-86.
 Journal code: 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199901
 ENTRY DATE: Entered STN: 19990128
 Last Updated on STN: 19990128
 Entered Medline: 19990113

AB In response to decreased cellular oxygen concentrations the basic helix-loop-helix (bHLH)/**PAS** (Per, Arnt, Sim) **hypoxia**-inducible transcription factor, HIF-1alpha, mediates activation of networks of target genes involved in angiogenesis, erythropoiesis and glycolysis. Here we demonstrate that the mechanism of activation of HIF-1alpha is a multi-step process which includes **hypoxia**-dependent nuclear import and activation (derepression) of the transactivation domain, resulting in recruitment of the CREB-binding protein (CBP)/p300 coactivator. Inducible nuclear accumulation was shown to be dependent on a nuclear localization signal (NLS) within the C-terminal end of HIF-1alpha which also harbors the **hypoxia**-inducible transactivation domain. Nuclear import of HIF-1alpha was inhibited by either deletion or a single amino acid substitution within the NLS sequence motif and, within the context of the full-length protein, these mutations also resulted in inhibition of the transactivation activity of HIF-1alpha and recruitment of CBP. However, nuclear localization per se was not sufficient for transcriptional activation, since fusion of HIF-1alpha to the heterologous GAL4 DNA-binding domain generated a protein which showed constitutive nuclear localization but required hypoxic stimuli for function as a CBP-dependent transcription factor. Thus, **hypoxia**-inducible nuclear import and transactivation by recruitment of CBP can be functionally separated from one another and play critical roles in signal transduction by HIF-1alpha.

L4 ANSWER 10 OF 20 MEDLINE DUPLICATE 9
 ACCESSION NUMBER: 1998298252 MEDLINE
 DOCUMENT NUMBER: 98298252 PubMed ID: 9632792
 TITLE: Role of the **PAS** domain in regulation of dimerization and DNA binding specificity of the dioxin receptor.
 AUTHOR: Pongratz I; Antonsson C; Whitelaw M L; **Poellinger L**
 CORPORATE SOURCE: Department of Cell and Molecular Biology, Karolinska Institutet, S-171-77 Stockholm, Sweden.
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1998 Jul) 18 (7) 4079-88.
 Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980723
Last Updated on STN: 19980723
Entered Medline: 19980716

AB The dioxin receptor is a ligand-regulated transcription factor that mediates signal transduction by dioxin and related environmental pollutants. The receptor belongs to the basic helix-loop-helix (bHLH)-Per-Arnt-Sim (**PAS**) family of factors, which, in addition to the bHLH motif, contain a **PAS** region of homology. Upon activation, the dioxin receptor dimerizes with the bHLH-**PAS** factor Arnt, enabling the receptor to recognize xenobiotic response elements in the vicinity of target genes. We have studied the role of the **PAS** domain in dimerization and DNA binding specificity of the dioxin receptor and Arnt by monitoring the abilities of the individual bHLH domains and different bHLH-**PAS** fragments to dimerize and bind DNA in vitro and recognize target genes in vivo. The minimal bHLH domain of the dioxin receptor formed homodimeric complexes, heterodimerized with full-length Arnt, and together with Arnt was sufficient for recognition of target DNA in vitro and in vivo. In a similar fashion, only the bHLH domain of Arnt was necessary for DNA binding specificity in the presence of the dioxin receptor bHLH domain. Moreover, the bHLH domain of the dioxin receptor displayed a broad dimerization potential, as manifested by complex formation with, e.g., the unrelated bHLH-Zip transcription factor USF. In contrast, a construct spanning the dioxin receptor bHLH domain and an N-terminal portion of the **PAS** domain failed to form homodimers and was capable of dimerizing only with Arnt. Thus, the **PAS** domain is essential to confer dimerization specificity of the dioxin receptor.

L4 ANSWER 11 OF 20 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 97303187 MEDLINE
DOCUMENT NUMBER: 97303187 PubMed ID: 9159130
TITLE: Activation of **hypoxia**-inducible factor 1alpha: posttranscriptional regulation and conformational change by recruitment of the Arnt transcription factor.
AUTHOR: Kallio P J; Pongratz I; Gradin K; McGuire J; **Poellinger L**
CORPORATE SOURCE: Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institutet, S-171 77 Stockholm, Sweden.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 May 27) 94 (11) 5667-72.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB In response to **hypoxia** the **hypoxia**-inducible factor-1 (HIF-1) mediates transcriptional activation of a network of genes encoding erythropoietin, vascular endothelial growth factor, and several glycolytic enzymes. HIF-1 consists of a heterodimer of two basic helix-loop-helix **PAS** (Per/Arnt/Sim) proteins, HIF-1alpha and Arnt. HIF-1alpha and Arnt mRNAs are constitutively expressed and were not altered upon exposure of HeLa or HepG2 cells to **hypoxia**, suggesting that the activity of the HIF-1alpha-Arnt complex may be regulated by some as yet unknown

posttranscriptional mechanism. In support of this model, we demonstrate here that Arnt protein levels were not increased under conditions that induce an hypoxic response in HeLa and HepG2 cells. However, under identical conditions, HIF-1alpha protein levels were rapidly and dramatically up-regulated, as assessed by immunoblot analysis. In addition, HIF-1alpha acquired a new conformational state upon dimerization with Arnt, rendering HIF-1alpha more resistant to proteolytic digestion in vitro. Dimerization as such was not sufficient to elicit the conformational change in HIF-1alpha, since truncated forms of Arnt that are capable of dimerizing with HIF-1alpha did not induce this effect. Moreover, the high affinity DNA binding form of the HIF-1alpha-Arnt complex was only generated by forms of Arnt capable of eliciting the allosteric change in conformation. In conclusion, the combination of enhanced protein levels and allosteric change by dimerization defines a novel mechanism for modulation of transcription factor activity.

L4 ANSWER 12 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1997:418838 BIOSIS
 DOCUMENT NUMBER: PREV199799718041
 TITLE: Regulation of cytochrome P4501A1 transcription by bHLH/
PAS transcription factors.
 AUTHOR(S): **Poellinger**, L.; Kallio, P.; Gradin, K.; Pongratz,
 I.; Wilson, W.; Antonsson, C.; McGuire, J.; Lindebro, M.;
 Dzeletovic, N.
 CORPORATE SOURCE: Dep. Cell Mol. Biol., Medical Nobel Inst., S-171 77
 Stockholm Sweden
 SOURCE: FASEB Journal, (1997) Vol. 11, No. 9, pp. A780.
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 ACCESSION NUMBER: 1998:405040 SCISEARCH
 THE GENUINE ARTICLE: ZK302
 TITLE: Regulation of cytochrome P4501A1 transcription by bHLH/
PAS transcription factors
 AUTHOR: **Poellinger L (Reprint)**; Kallio P; Gradin K;
 Pongratz I; Wilson W; Antonsson C; McGuire J; Lindebro M;
 Dzeletovic N
 CORPORATE SOURCE: MED NOBEL INST, DEPT CELL & MOL BIOL, S-17177 STOCKHOLM,
 SWEDEN
 COUNTRY OF AUTHOR: SWEDEN
 SOURCE: FASEB JOURNAL, (31 JUL 1997) Vol. 11, No. 9,
 Supp. [S], pp. P57-P57.
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 PIKE, BETHESDA, MD 20814-3998.
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L4 ANSWER 14 OF 20 MEDLINE DUPLICATE 11
 ACCESSION NUMBER: 96413273 MEDLINE
 DOCUMENT NUMBER: 96413273 PubMed ID: 8816435
 TITLE: Functional interference between **hypoxia** and
 dioxin signal transduction pathways: competition for
 recruitment of the Arnt transcription factor.
 AUTHOR: Gradin K; McGuire J; Wenger R H; Kvietikova I; fhitelaw M

L; Toftgard R; Tora L; Gassmann M; **Poellinger L**
 CORPORATE SOURCE: Department of Medical Nutrition, Karolinksa Institute, Huddinge, Sweden.
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1996 Oct) 16 (10) 5221-31.
 Journal code: 8109087. ISSN: 0270-7306.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199611
 ENTRY DATE: Entered STN: 19961219
 Last Updated on STN: 19961219
 Entered Medline: 19961115

AB **Hypoxia**-inducible factor 1 alpha (HIF-1 alpha) and the intracellular dioxin receptor mediate **hypoxia** and dioxin signalling, respectively. Both proteins are conditionally regulated basic helix-loop-helix (bHLH) transcription factors that, in addition to the bHLH motif, share a Per-Arnt-Sim (**PAS**) region of homology and form heterodimeric complexes with the common bHLH/**PAS** partner factor Arnt. Here we demonstrate that HIF-1 alpha required Arnt for DNA binding in vitro and functional activity in vivo. Both the bHLH and **PAS** motifs of Arnt were critical for dimerization with HIF-1 alpha. Strikingly, HIF-1 alpha exhibited very high affinity for Arnt in coimmunoprecipitation assays in vitro, resulting in competition with the ligand-activated dioxin receptor for recruitment of Arnt. Consistent with these observations, activation of HIF-1 alpha function in vivo or overexpression of HIF-1 alpha inhibited ligand-dependent induction of DNA binding activity by the dioxin receptor and dioxin receptor function on minimal reporter gene constructs. However, HIF-1 alpha- and dioxin receptor-mediated signalling pathways were not mutually exclusive, since activation of dioxin receptor function did not impair HIF-1 alpha-dependent induction of target gene expression. Both HIF-1 alpha and Arnt mRNAs were expressed constitutively in a large number of human tissues and cell lines, and these steady-state expression levels were not affected by exposure to **hypoxia**. Thus, HIF-1 alpha may be conditionally regulated by a mechanism that is distinct from induced expression levels, the prevalent model of activation of HIF-1 alpha function. Interestingly, we observed that HIF-1 alpha was associated with the molecular chaperone hsp90. Given the critical role of hsp90 for ligand binding activity and activation of the dioxin receptor, it is therefore possible that HIF-1 alpha is regulated by a similar mechanism, possibly by binding an as yet unknown class of ligands.

L4 ANSWER 15 OF 20 MEDLINE DUPLICATE 12
 ACCESSION NUMBER: 96125126 MEDLINE
 DOCUMENT NUMBER: 96125126 PubMed ID: 8537407
 TITLE: The basic helix-loop-helix/**PAS** factor Sim is associated with hsp90. Implications for regulation by interaction with partner factors.
 AUTHOR: McGuire J; Coumailleau P; Whitelaw M L; Gustafsson J A; **Poellinger L**
 CORPORATE SOURCE: Department of Medical Nutrition, Karolinska Institute, Huddinge, Sweden.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Dec 29) 270 (52) 31353-7.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199602
 ENTRY DATE: Entered STN: 19960221
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Entered Medline: 19960208

AB Sim is a Drosophila developmental basic helix-loop-helix (bHLH) transcription factor containing a Per-Arnt-Sim (PAS) region of homology. Here we demonstrate that Sim, in analogy to the structurally related bHLH/PAS dioxin receptor, was stably associated with the molecular chaperone hsp90. In the case of the dioxin receptor, release of hsp90 and derepression of receptor function appear to be regulated by ligand binding and dimerization with Arnt, a non-hsp90-associated bHLH/PAS factor. Dimerization with Arnt very efficiently disrupted Sim-hsp90 interaction, a process that required both the bHLH and PAS dimerization motifs of Arnt. Moreover, hsp90 was also released upon dimerization of Sim with the Drosophila PAS factor Per, whereas the hsp90-associated dioxin receptor failed to interact with Sim. These results indicate that hsp90 may play a role in conditional regulation of Sim function, and that Per and possibly bHLH/PAS partner factors may activate Sim by inducing release of hsp90 during the dimerization process.

L4 ANSWER 16 OF 20 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 96027642 MEDLINE
DOCUMENT NUMBER: 96027642 PubMed ID: 7559670
TITLE: Definition of a minimal domain of the dioxin receptor that is associated with Hsp90 and maintains wild type ligand binding affinity and specificity.
AUTHOR: Coumailleau P; Poellinger L; Gustafsson J A; Whitelaw M L
CORPORATE SOURCE: Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital F-60, Sweden.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Oct 20) 270 (42) 25291-300.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951121

AB The dioxin receptor is a cytoplasmic basic helix-loop-helix/Per-Arnt-Sim homology (bHLH/PAS) protein known to bind planar polycyclic ligands including polycyclic aromatic hydrocarbons, benzoflavones, heterocyclic amines, and halogenated aromatic hydrocarbons, e.g. dioxins. Ligand-induced activation of the dioxin receptor initiates a process whereby the receptor is transformed into a nuclear transcription factor complex with a specific bHLH/PAS partner protein, Arnt. In analogy to the glucocorticoid receptor, the latent dioxin receptor is found associated with the molecular chaperone hsp90. We have defined and isolated a minimal ligand binding domain of the dioxin receptor from the central PAS region, comprising of amino acids 230 to 421, and found this domain to interact with hsp90 in vitro. Expression of the minimal ligand binding domain in wheat germ lysates or bacteria, systems which harbor hsp90 homologs unable to interact with the glucocorticoid or dioxin receptors, resulted in non-ligand binding forms of this minimal 230 to 421 fragment. Importantly, affinity of the minimal ligand binding domain for dioxin was similar to the affinity inherent in the full-length dioxin receptor, and a profile of ligand structures which specifically bound the minimal ligand binding domain was found to be conserved between this domain and the native receptor. These experiments show that the minimal ligand binding domain maintains the quantitative and qualitative aspects of ligand binding exhibited by the full-length receptor, implying that the central ligand binding pocket may exist to accommodate all classes of specific dioxin receptor ligands, and that this pocket is critically dependent upon hsp90 for its ligand binding conformation.

L4 ANSWER 17 OF 20 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 95293999 MEDLINE
DOCUMENT NUMBER: 95293999 PubMed ID: 7775458
TITLE: Constitutive function of the basic helix-loop-helix/
PAS factor Arnt. Regulation of target promoters via
the E box motif.
AUTHOR: Antonsson C; Arulampalam V; Whitelaw M L; Pettersson S;
Poellinger L
CORPORATE SOURCE: Department of Medical Nutrition, Karolinska Institute,
Novum, Huddinge, Sweden.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Jun 9) 270
(23) 13968-72.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19950720
Entered Medline: 19950710

AB Arnt is a nuclear basic helix-loop-helix (bHLH) transcription factor that,
contiguous with the bHLH motif, contains a region of homology (**PAS**
) with the Drosophila factors Per and Sim. Arnt dimerizes in a
ligand-dependent manner with the bHLH dioxin receptor, a process that
enables the dioxin-(2,3,7,8-tetrachlorodibenzo-p-dioxin)-activated
Arnt-dioxin receptor complex to recognize dioxin response elements of
target promoters. In the absence of dioxin, Arnt does not bind to this
target sequence motif. The constitutive function of Arnt is presently not
understood. Here we demonstrate that Arnt constitutively bound the E box
motif CACGTG that is also recognized by a number of distinct bHLH factors,
including USF and Maximum Importantly, amino acids that have been identified
to be critical for E box recognition by Max and USF are conserved in Arnt.
Consistent with these observations, full-length Arnt, but not an Arnt
deletion mutant lacking its potent C-terminal transactivation domain,
constitutively activated CACGTG E box-driven reporter genes in vivo. These
results indicate a role of Arnt in regulation of a network of target genes
that is distinct from that regulated by the Arnt-dioxin receptor complex
in dioxin-stimulated cells.

L4 ANSWER 18 OF 20 MEDLINE DUPLICATE 15

ACCESSION NUMBER: 95354671 MEDLINE
DOCUMENT NUMBER: 95354671 PubMed ID: 7628454
TITLE: Protein-protein interaction via **PAS** domains: role
of the **PAS** domain in positive and negative
regulation of the bHLH/**PAS** dioxin receptor-Arnt
transcription factor complex.
AUTHOR: Lindebro M C; **Poellinger L**; Whitelaw M L
CORPORATE SOURCE: Department of Medical Nutrition, Karolinska Institute,
Huddinge University Hospital, Sweden.
SOURCE: EMBO JOURNAL, (1995 Jul 17) 14 (14) 3528-39.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19970203
Entered Medline: 19950907

AB Gene regulation by dioxins is mediated by the dioxin receptor-Arnt
heterodimer, a ligand generated complex of two basic helix-loop-helix
(bHLH)/Per-Arnt-Sim (**PAS**) transcription factors. By using dioxin

receptor chimeras where the dimerization and DNA binding bHLH motif has been replaced by a heterologous DNA binding domain, we have detected an ability of Arnt to interact with the dioxin receptor via the **PAS** domain in a mammalian 'hybrid interaction' system. By coimmunoprecipitation assays, we have confirmed the ability of **PAS** domains of the dioxin receptor and Arnt to mediate independent heterodimerization in vitro. Selectivity for **PAS** dimerization was noted in our hybrid interaction system, as dioxin receptor or Arnt **PAS**-mediated homodimers were not detected. Surprisingly, however, the **PAS** domain of Per could dimerize with both the dioxin receptor and Arnt subunits in vitro, and disrupt the ability of these subunits to form a DNA binding heterodimer. Moreover, ectopic expression of Per blocked dioxin signalling in mammalian cells. The **PAS** domains of the dioxin receptor and Arnt are therefore novel dimerizing regions critical in formation of a functional dioxin receptor-Arnt complex, while the PerPAS domain is a potential negative regulator of bHLH/**PAS** factor function.

L4 ANSWER 19 OF 20 MEDLINE DUPLICATE 16

ACCESSION NUMBER: 95124333 MEDLINE
DOCUMENT NUMBER: 95124333 PubMed ID: 7823943
TITLE: Distinct roles of the molecular chaperone hsp90 in modulating dioxin receptor function via the basic helix-loop-helix and **PAS** domains.
AUTHOR: Antonsson C; Whitelaw M L; McGuire J; Gustafsson J A; Poellinger L
CORPORATE SOURCE: Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital, Novum, Sweden.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1995 Feb) 15 (2) 756-65.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19970203
Entered Medline: 19950216

AB The intracellular dioxin receptor mediates signal transduction by dioxin and functions as a ligand-activated transcription factor. It contains a basic helix-loop-helix (bHLH) motif contiguous with a Per-Arnt-Sim (**PAS**) homology region. In extracts from nonstimulated cells the receptor is recovered in an inducible cytoplasmic form associated with the 90-kDa heat shock protein (hsp90), a molecular chaperone. We have reconstituted ligand-dependent activation of the receptor to a DNA-binding form by using the dioxin receptor and its bHLH-**PAS** partner factor Arnt expressed by in vitro translation in reticulocyte lysate. Deletion of the **PAS** domain of the receptor resulted in constitutive dimerization with Arnt. In contrast, this receptor mutant showed low levels of xenobiotic response element-binding activity, indicating that the **PAS** domain may be important for DNA-binding affinity and/or specificity of the receptor. It was not possible to reconstitute dioxin receptor function with proteins expressed in wheat germ lysate. In line with these observations, reticulocyte lysate but not wheat germ lysate promoted the association of de novo synthesized dioxin receptor with hsp90. At least two distinct domains of the receptor mediated interaction with hsp90: the ligand-binding domain located within the **PAS** region and, surprisingly, the bHLH domain. Whereas ligand-binding activity correlated with association with hsp90, bHLH-hsp90 interaction appeared to be important for DNA-binding activity but not for dimerization of the receptor. Several distinct roles for hsp90 in modulating dioxin receptor function are therefore likely: correct folding of the ligand-binding domain, interference with Arnt heterodimerization,

and folding of a DNA-binding conformation of the bHLH domain. Thus, the dioxin receptor system provides a complex and interesting model of the regulation of transcription factors by hsp90.

L4 ANSWER 20 OF 20 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 95059063 MEDLINE
DOCUMENT NUMBER: 95059063 PubMed ID: 7969169
TITLE: Identification of transactivation and repression functions of the dioxin receptor and its basic helix-loop-helix/
PAS partner factor Arnt: inducible versus constitutive modes of regulation.
AUTHOR: Whitelaw M L; Gustafsson J A; **Poellinger L**
CORPORATE SOURCE: Center for Biotechnology, Karolinska Institutet, Huddinge University Hospital, Sweden.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1994 Dec) 14 (12) 8343-55.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19970203
Entered Medline: 19941220
AB Gene regulation by dioxins is mediated via the dioxin receptor, a ligand-dependent basic helix-loop-helix (bHLH)/**PAS** transcription factor. The latent dioxin receptor responds to dioxin signalling by forming an activated heterodimeric complex with a specific bHLH partner, Arnt, an essential process for target DNA recognition. We have analyzed the transactivating potential within this heterodimeric complex by dissecting it into individual subunits, replacing the dimerization and DNA-binding bHLH motifs with heterologous zinc finger DNA-binding domains. The uncoupled Arnt chimera, maintaining 84% of Arnt residues, forms a potent and constitutive transcription factor. Chimeric proteins show that the dioxin receptor also harbors a strong transactivation domain in the C terminus, although this activity was silenced by inclusion of 82 amino acids from the central ligand-binding portion of the dioxin receptor. This central repression region conferred binding of the molecular chaperone hsp90 upon otherwise constitutive chimeras in vitro, indicating that hsp90 has the ability to mediate a cis-repressive function on distant transactivation domains. Importantly, when the ligand-binding domain of the dioxin receptor remained intact, the ability of this hsp90-binding activity to confer repression became conditional rather than irreversible. Our data are consistent with a model in which crucial activities of the dioxin receptor, such as dimerization with Arnt and transactivation, are conditionally repressed by the central ligand- and-hsp90-binding region of the receptor. In contrast, the Arnt protein appears to be free from any repressive activity. Moreover, within the context of the dioxin response element (xenobiotic response element), the C terminus of Arnt conferred a potent, dominating transactivation function onto the native bHLH heterodimeric complex. Finally, the relative transactivation potencies of the individual dioxin receptor and Arnt chimeras varied with cell type and promoter architecture, indicating that the mechanisms for transcriptional activation may differ between these two subunits and that in the native complex the transactivation pathway may be dependent upon cell-specific and promoter contexts.